

Docket No.: PF-0530-1 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure  
Examining Group 1642

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By: *Lisa McDill* Printed: Lisa McDill

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: Hillman et al.

Title: HUMAN GLUTATHIONE PEROXIDASE-6

Serial No.: 09/811,118

Filing Date: March 16, 2001

Examiner: Yaen, C.H.

Group Art Unit: 1642

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P.O. Box 1450  
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**BRIEF ON APPEAL**

Sir:

Further to the Notice of Appeal filed August 21, 2003, and received at the Patent Office on August 25, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the \$330 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 3-6, 9-11, 38, 39, 42, and 43 of the above-identified application.

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**(1) REAL PARTY IN INTEREST**

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation), (Reel 9569, Frame 0041) which is the real party in interest herein.

**(2) RELATED APPEALS AND INTERFERENCES**

Appellants, their legal representative and the assignee are not aware of any other related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

**(3) STATUS OF THE CLAIMS**

Claims rejected: Claims 3-6, 9-11, 38, 39, 42, and 43  
Claims allowed: none  
Claims canceled: Claims 8, 15-19, and 22-37  
Claims withdrawn: Claims 1, 2, 7, 12-14, 20, 21, 40, and 41  
Claims on Appeal: Claims 3-6, 9-11, 38, 39, 42, and 43 (A copy of the claims on appeal, as amended, can be found in the attached Appendix.)

**(4) STATUS OF AMENDMENTS AFTER FINAL**

No amendments were submitted after Final Rejection.

**(5) SUMMARY OF THE INVENTION**

Appellants' invention is directed to polynucleotides, including polynucleotides comprising the polynucleotide sequence of SEQ ID NO:2, encoding glutathione peroxidase GPx6, comprising the amino acid sequence of SEQ ID NO:1 (Specification, e.g., at page 2, line 32 to page 3, line 3; page 4, lines 29-31; page 13, lines 5-7; and page 13, line 33 to page 14, line 1). Appellants' invention also includes polynucleotides encoding a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:1 (e.g., at page 3, lines 4-10; and page 13, lines 29-33), polynucleotides encoding fragments of SEQ ID NO:1 (e.g., at page 3, lines 6-7; and page 6, lines 24-27), polynucleotides

comprising a naturally occurring polynucleotide sequence at least 90% identical to SEQ ID NO:2 (e.g., at page 3, lines 16-22; and page 14, lines 2-9), and fragments of the foregoing polynucleotides (e.g., at page 3, lines 16-22; and page 11, lines 16-20). The invention further includes recombinant polynucleotides comprising the foregoing polynucleotides (e.g., at page 18, lines 10-33), and host cells comprising the foregoing polynucleotides (e.g., at page 19, lines 1-8).

GPx6, encoded by polynucleotides of the invention, has strong chemical and structural homology to human phospholipid hydroperoxide glutathione peroxidase GPx4 (GenBank ID 544432; SEQ ID NO:3) (Specification, e.g., at page 13, lines 21-23). In particular, GPx6 and human phospholipid hydroperoxide glutathione peroxidase GPx4 share 40% sequence identity, and have similar molecular weights (20.9 kD and 19.5 kD, respectively) and isoelectric points (7.79 and 7.88, respectively) (e.g., at page 13, lines 23-25; and Figure 2). In addition:

“GPx6 is 187 amino acids in length and has three potential casein kinase II phosphorylation sites at residues S96, S136, and S164; two potential protein kinase C phosphorylation sites at S96 and S136; and a glutathione peroxidase signature at L82. PFAM identifies significant sequence identity with glutathione peroxidase. BLOCKS identifies significant sequence identity with glutathione peroxidase over residues 35-60, 63-100, 107-133, and 138-159, which includes the glutathione peroxidase catalytic triad formed by residues Cys57, Gln92, and Trp142. . . Northern analysis shows the expression of this sequence in various libraries, at least 38% of which are immortalized or cancerous, at least 33% of which are associated with fetal development and cell proliferation, and at least 14% of which involve immune response. Of particular note is the expression of GPx6 in nervous, reproductive, and developmental tissues.”  
(Specification at page 13, lines 15-28)

The polynucleotides of the present invention are useful, for example, for toxicology testing, drug discovery, disease diagnosis, and chromosomal mapping (Specification, e.g., at page 32, lines 17-25; page 33, lines 28-34; page 37, lines 6-11; and page 37, line 17 to page 38, line 11).

#### (6) ISSUES

1. Whether claims 3-6, 9-11, 38, 39, 42, and 43 meet the utility requirement of 35 U.S.C. § 101.

2. Whether claims 3-6, 9-11, 38, 39, 42, and 43 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

Appellants respectfully note that the Examiner has indicated that the enablement rejections of claims 3-6, 9-11, and 38-39 under 35 U.S.C. § 112, first paragraph; the indefiniteness rejections of claims 3-6 and 38 under 35 U.S.C. § 112, second paragraph; and the anticipation rejection of claim 3 under 35 U.S.C. § 102(a), have been withdrawn (Office Action, May 23, 2003; page 2, §§ 5-6). However, the Examiner includes the phrase “Claim Rejections Maintained” in the headings of the paragraphs indicating withdrawal of these rejections. Since no arguments have been presented to support the maintenance of these rejections, Appellants assume that the use of the phrase “Claim Rejections Maintained” in the paragraph headings was an inadvertent typographical error. Therefore, Appellants are proceeding under the assumption that these rejections have been withdrawn.

#### (7) GROUPING OF THE CLAIMS

##### **As to Issue 1**

All of the claims on appeal are grouped together.

##### **As to Issue 2**

Claims 3, 5, 6, 9, 11, 39, and 43 are grouped together, and claims 4, 10, 38, and 42 are grouped together.

#### (8) APPELLANTS’ ARGUMENTS

##### **Issue 1 – Whether the claims on appeal meet the utility requirement of 35 U.S.C. § 101**

Claims 3-6, 9-11, 38, 39, 42, and 43 stand rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well-established utility (Office Action, May 23, 2003; page 3). These rejections allege in particular that:

“the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Bork . . . states that the error rate of functional annotations in the sequence database is considerable, making it even

more difficult to infer correct function from a structural comparison of a new sequence with a sequence database . . . Bowie et al. . . . state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex . . . Thus, the specification fails to support the asserted credible, specific and substantial utility of hydroperoxide glutathione peroxidase activity.” (Office Action, May 23, 2003; page 3)

and

“without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean. . . The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides.” (Office Action, May 23, 2003; pages 4-5)

**The rejection of claims 3-6, 9-11, 38, 39, 42, and 43 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.**

The invention at issue is a polynucleotide corresponding to a gene that is expressed in reproductive, neurological, immortalized, cancerous, developmental, and immune response-related tissues of humans (Specification, e.g., at page 13, lines 25-28; and page 23, lines 28-30). The claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the glutathione peroxidase family, whose biological functions include breaking down hydrogen peroxide and hydroperoxides within cells (e.g., at page 1, line 29 to page 2, line 4; page 13, lines 21-25; and Figure 2). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants submit with this brief the declaration of Dr. Tod Bedilion (of record; originally submitted on February 6, 2003) describing some of the practical uses of the claimed invention in gene

and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as highly specific probes in a cDNA microarray:

Persons skilled in the art would [on June 1, 1998] appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer, for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15)

The Patent Examiner does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Examiner contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological functions, or the biological functions of their encoded polypeptide. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the protein encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise biological functions.

The Examiner alleges that the asserted utility of the claimed polynucleotides in toxicology testing is not specific and substantial because "[a]bsent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery and toxicology testing" (Office Action, May 23, 2003; page

5). This is incorrect. The claimed polynucleotides can be used for toxicology testing in drug discovery without any knowledge of biological function or disease association. Monitoring the expression of the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide, or to a polypeptide encoded by such a polynucleotide, regardless of the disease association or biological function of the claimed polynucleotides. The claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides and polypeptides, regardless of any possible utility for measuring properties of the claimed polynucleotides themselves.

Furthermore, while it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific, substantial, and credible. A toxicology test using any particular expressed polynucleotide is dependent on the identity of that polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. No two human-expressed polynucleotides are interchangeable for toxicology testing because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the identities of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, it is not necessary to provide “a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue” for the claimed polynucleotides to have a specific and substantial utility in toxicology testing. At the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

## **I. The Applicable Legal Standard**

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is “practically useful,” *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a “specific benefit” on the public. *Brenner v.*

*Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is “useful” under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) (“to violate Section 101 the claimed device must be totally incapable of achieving a useful result”); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention “is incapable of serving any beneficial end”).

*Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a “nebulous expression” such as “biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a “well-established” utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is



no “well-established” utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Examiner bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Examiner must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Examiner makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

**II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph**

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are “well-established” uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application’s specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Examiner, further corroborates the credibility of the asserted utilities.

**A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer “specific benefits” to the public**

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA

microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotides.

The instant application is a divisional of, and claims priority to, Hillman et al. (U.S. Ser. No. 09/088,549, filed June 1, 1998; hereinafter “the Hillman ‘549 application”). The instant application and the Hillman ‘549 application were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the instant application and the Hillman ‘549 application.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Hillman ‘549 application on June 1, 1998 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as highly specific probes for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion’s explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration at, e.g., ¶¶ 12 and 15).<sup>1</sup>

In connection with his explanations, Dr. Bedilion states that “the specification of the Hillman ‘549 application would have led a person skilled in the art on June 1, 1998, who was using gene expression monitoring in connection with developing new drugs for the treatment of reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer, to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides” (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, “[p]ersons skilled in the art would [on June 1, 1998] appreciate

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<sup>1</sup>Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Hillman ‘549 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer, for such purposes as evaluating their efficacy and toxicity.” *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-June 1, 1998 publications showing the state of the art on June 1, 1998 (Bedilion Declaration at, e.g., ¶¶ 10-14). While Dr. Bedilion’s explanations in paragraph 15 of his Declaration include over three pages of text and six subparts (a)-(f), he specifically states that his explanations are not “all-inclusive.” *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on June 1, 1998 (and for several years prior to June 1, 1998) “without any doubt” appreciated that the toxicity (or lack of toxicity) of any proposed drug was “one of the most important criteria to be considered and evaluated in connection with the development of the drug” and how the teachings of the Hillman ‘549 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Hillman ‘549 application at the time it was filed “would have wanted their cDNA microarray to have a probe to a SEQ ID NO:1-encoding polynucleotide because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 1, 1998” (Bedilion Declaration, ¶ 15, item (f) ). This, by itself, provides more than sufficient reason to compel the conclusion that the Hillman ‘549 application disclosed to persons skilled in the art at the time of its filing substantial, specific, and credible real-world utilities for the claimed polynucleotides.

Nowhere does the Patent Examiner address the fact that, as described, for example, on pages 37 and 45-46 of the Hillman ‘549 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to

measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed SEQ ID NO:2 polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); M.P.E.P. § 2107.01 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., **they are useful in analyzing compounds**)" (emphasis added) ).

Though Appellants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as cancerous and immortalized cells (see the Hillman '549 application at, e.g., page 13, lines 24-27), there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential drug candidate for reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer, or potential toxin, with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f) ).

The Bedilion Declaration shows that a number of pre-June 1, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Hillman '549 application was filed (Bedilion Declaration at, e.g.,

¶¶ 10-14; and Tabs A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Declaration at Tab D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

The Brown '522 patent further teaches that the “[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention” can be used in “numerous” genetic applications, including “monitoring of gene expression” applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58; and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Hillman '549 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.

\* \* \*

Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

\* \* \*

Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a **pattern** of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the unknown

and the standard, thereby providing a platform for more extensive toxicological examination. [emphasis in original]

Rockett et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems and potential, Xenobiotica, 1999, 29:655-691.

In another article, Lashkari et al. state explicitly that sequences that are merely “predicted” to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. **The amplicons can also be used directly by, for example, arraying onto glass for expression analysis**, for DNA binding assays, or for any direct DNA assay. [emphasis added]

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proceedings of the National Academy of Sciences USA, 1997, 94:8945-8947.

**B. The use of polynucleotides coding for polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now “well-established”**

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett et al., *supra*:

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the

developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis, 1999, 24:153-159; Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology – potentials and limitations, Toxicology Letters, 2000, 112-113:467-471.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. “Arrays are at their most powerful when they contain the entire genome of the species they are being used to study.” John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environmental Health Perspectives, 1999, 107:681-685. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be overturned regardless of their merit.

**C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility**

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotides can be imputed based on the relationship between the polypeptide they encode, GPx6, and another polypeptide of unquestioned utility, human phospholipid hydroperoxide glutathione peroxidase (GPx4). The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility



similar to GPx4. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the polypeptide coded for by the claimed polynucleotides shares 40% sequence identity over 187 amino acid residues with GPx4 (Specification, e.g., at page 13, lines 23-25; and Figure 2). In addition, GPx6 and GPx4 have similar molecular weights (20.9 kD and 19.5 kD, respectively) and isoelectric points (7.79 and 7.88, respectively) (e.g., at page 13, lines 23-25). This is more than enough homology to demonstrate a reasonable probability that the utility of GPx4 can be imputed to the polynucleotides of the claimed invention (through the polypeptide they encode). It is well-known that the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues is exceedingly small. Brenner et al., Proceedings of the National Academy of Sciences USA, 1998, 95:6073-6078. Given homology in excess of 30% over more than 150 amino acid residues, the probability that the polypeptide coded for by the claimed polynucleotides is related to GPx4 is, accordingly, very high. Moreover, "PFAM identifies significant sequence identity with glutathione peroxidase" and "BLOCKS identifies significant sequence identity with glutathione peroxidase over residues 35-60, 63-100, 107-133, and 138-159, which includes the glutathione peroxidase catalytic triad formed by residues Cys57, Gln92, and Trp142" (Specification, e.g., at page 13, lines 18-21). In combination, these facts provide more than enough evidence to demonstrate a reasonable probability that the utility of glutathione peroxidases can be imputed to the claimed invention (through the polypeptide they encode).

The Examiner must accept the Appellants' demonstration that the homology between the polypeptide coded for by the claimed invention and GPx4 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Bowie et al., Science, 1990, 247:1306-1310; Burgess et al., J. Cell Biol.,

1990, 111:2129-2138; Scott et al., Nat. Genet., 1999, 21:440-443; Bork, Genome Res., 2000, 10:398-400. Importantly, none contradicts Brenner's basic rule that sequence homology in excess of 30% over 150 or more amino acid residues yields a high probability of functional homology as well. Brenner et al., Proceedings of the National Academy of Sciences USA, 1998, 95:6073-6078. In addition, none contradicts Bork's findings in the Bork reference, cited by the Examiner, that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology. Bork, *supra*. Furthermore, nor do these articles contradict the fact that the identification of the polypeptide encoded by the claimed polynucleotides using a combination of independent methods provides compelling scientific evidence that the polypeptide has the functions of a glutathione peroxidase. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

**D. Objective evidence corroborates the utilities of the claimed invention**

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its

database containing the sequences of the claimed polynucleotides and the encoded polypeptide, and millions of other sequences, throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the claimed polynucleotides, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

### **III. The Patent Examiner's rejections are without merit**

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not "credible, specific and substantial" utilities (Office Action, May 23, 2003; page 3). The Examiner is incorrect both as a matter of law and as a matter of fact.

#### **A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility**

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the Appellants provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is

not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an “identifiable benefit” in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, e.g., ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called “throwaway” utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

**B. Membership in a class of useful products can be proof of utility**

Despite the evidence that the claimed polynucleotides encode a polypeptide in the glutathione peroxidase family, the Examiner refused to impute the utility of the members of the glutathione peroxidase family to GPx6. In the Office Action of May 23, 2003, the Examiner takes the position that, unless Appellants can identify which particular biological function within the class of glutathione

peroxidases is possessed by GPx6, utility cannot be imputed. To demonstrate utility by membership in the class of glutathione peroxidase proteins, the Examiner would require that all glutathione peroxidase proteins possess a “common” utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. See *Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a “general” class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses GPx6 as if the general class in which it is included is not the glutathione peroxidase family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these “general classes” may contain a substantial number of useless members, the glutathione peroxidase family does not. The glutathione peroxidase family is sufficiently specific to rule out any reasonable possibility that GPx6 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the class of glutathione peroxidase proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a “substantial likelihood” that the GPx6 encoded by the claimed polynucleotides is useful. It follows that the SEQ ID NO:2 polynucleotide also is useful.

Even if the Examiner’s “common utility” criterion were correct – and it is not – the glutathione peroxidase family would meet it. It is undisputed that known members of the glutathione peroxidase

family are proteins involved in the breakdown of hydrogen peroxide and hydroperoxides within cells. A person of ordinary skill in the art need not know any more about how the claimed invention participates in the breakdown of hydrogen peroxide and hydroperoxides within cells to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given glutathione peroxidase breaks down any particular hydroperoxide within cells. The Examiner then goes on to assume that the only use for GPx6 absent knowledge as to how the glutathione peroxidase protein actually works is further study of GPx6 itself.

Not so. As demonstrated by Appellants, knowledge that GPx6 is a glutathione peroxidase protein is more than sufficient to make it useful for the diagnosis and treatment of reproductive and immune disorders, and cell proliferative disorders including developmental disorders and cancer. Indeed, GPx6 has been shown to be expressed in immortalized, cancerous, neurological, reproductive, developmental, cell proliferation-related, and immune response-related tissues of humans. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

**C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself**

The Examiner's rejection of the claims at issue is tantamount to a rejection on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be reversed.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107.01):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between

inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the Patent Office's Training Materials to be useful, as are polynucleotide sequences used, for example, as markers.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete (Bedilion Declaration at ¶ 15).

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any

particular expressed polynucleotide is dependent on the identity of that polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. **No two human-expressed polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the identities of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

As an example, any histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes**. A drug candidate which alters expression of a histone gene is toxic because disruption of such a pervasively-expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of a histone gene is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene in toxicology testing is specific and substantial because a toxicology test using that histone gene cannot be replaced by a toxicology test using a different gene, including any other histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene.

The claimed invention has numerous additional uses as a research tool, each of which alone is a “substantial utility.” These include diagnostic assays (Specification, e.g., at pages 35-36), chromosomal mapping (e.g., at pages 37-38), etc.



**D. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention**

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the Appellants cannot impute utility to the claimed invention based on the 40% identity between the encoded polypeptide, GPx6, and another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.C, *supra*, the literature cited by the Examiner is not inconsistent with the Appellants' proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. Under the applicable law, once the Appellants demonstrate a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

In the present case, the Examiner contends that the degree of amino acid identity among GPx6 and other glutathione peroxidase proteins is insufficient to establish that GPx6 is a member of the glutathione peroxidase family and thus shares the same utilities. The Examiner attempted to support this assertion with the teachings of Bowie et al. (Science, 1990, 247:1306-1310), Burgess et al. (J. Cell Biol., 1990, 111:2129-2138), Scott et al. (Nat. Genet., 1999, 21:440-443), and Bork (Genome Res., 2000, 10:398-400), all of record and addressed below. However, all of these references fail to support the outstanding rejections.

Appellants submit that the teachings of Bowie et al. are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of GPx6 based on amino acid sequence homology to glutathione peroxidases. Careful review of this reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein

structure and function. As discussed below in further detail, such experiments are not relevant to Appellants' use of amino acid sequence homology to reasonably predict protein function.

In support of Appellants' use of amino acid sequence homology to reasonably predict the utility of the polypeptide encoded by the claimed polynucleotides, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph). It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Appellants submit that the amino acid differences among the polypeptide encoded by Appellants' claimed polynucleotides and known glutathione peroxidases are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would further conclude that the level of conservation observed between the polypeptide encoded by Appellants' claimed polynucleotides and glutathione peroxidases is indicative of a common function, and hence, common utility, among these proteins.

In further support of Appellants' use of amino acid sequence homology to reasonably predict the biological function of the polypeptide encoded by the claimed polynucleotides, Appellants provide the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., page 6076). As demonstrated by the sequence alignment between GPx6 (Incyte ID No. 1817518; SEQ ID NO:1) and human phospholipid hydroperoxide glutathione peroxidase GPx4 (GenBank ID No. g544432; SEQ ID NO:3) shown in Figure 2, these two proteins

share 40% identity over 187 amino acids (Specification, e.g., at page 13, lines 21-25), thus meeting the criteria of Brenner et al. Therefore, SEQ ID NO:1 and human phospholipid hydroperoxide glutathione peroxidase GPx4 share sequence identity that exceeds the thresholds proposed by Brenner et al. Thus, SEQ ID NO:1 is a true phospholipid hydroperoxide glutathione peroxidase homolog by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of human phospholipid hydroperoxide glutathione peroxidase GPx4. Hence, the “reasonable correlation” standard as set by case law has been met.

The use of such sequence comparisons to predict protein function is supported by the Bork reference, cited by the Examiner. The Bork reference discloses a 70% accuracy rate in bioinformatics-based predictions. This more than meets the legal standard of utility, which requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% accuracy rate for all bioinformatics predictions.

The Examiner further cited Burgess et al. as demonstrating that even a single amino acid change can alter protein function. However, this reference is not relevant to the case at hand. Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In this case, a particular amino acid residue with known importance to protein function was specifically targeted for site-directed mutagenesis. This mutation was “artificially” created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutation described by Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences between SEQ ID NO:1 and human phospholipid hydroperoxide glutathione peroxidase GPx4 are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of Burgess et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Examiner's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated. Furthermore, in those rare cases where a partial loss-of-function mutation is persistent, the fact remains that the mutant polypeptide **still retains the utility of the non-mutant polypeptide**. The utility of the mutant polypeptide is the same as that of the non-mutant polypeptide, even though the results achieved are not equivalent. **Some** utility, not **perfect** utility, is all that is statutorily required for patentable utility.

The Examiner cited Scott et al. as further evidence that functional prediction by sequence homology is not reliable. Scott et al. describe a single example in which sequence homology was only partially successful in predicting the protein function of pendrin. In this example, pendrin was correctly identified as an anion transporter by sequence homology. However, the assignment of sulfate as a substrate for pendrin was later found to be incorrect. This one single example of a partially-incorrect functional prediction does not contradict the findings of Bork that, in the majority of cases, protein function is accurately predicted by sequence homology methods. Thus, Scott et al. does not provide any evidence that one of skill in the art would **more likely than not** doubt that GPx6 possesses the utilities of glutathione peroxidases.

The Examiner uses the teachings of Bork to assert that "the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database" (Office Action, May 23, 2003; page 3). In spite of any errors that may exist in the public sequence databases, Bork has shown that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology (Bork, Table 1 on page 399). The legal standard for utility requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. Therefore, the disclosure in Bork of a 90% accuracy rate for the prediction of

functional features by homology shows that such methods are more than adequate for supporting a patentable utility.

The references cited by the Examiner show that there may be difficulties and errors involved in predicting protein function by homology. However, these references do not contradict the fact that such methods are accurate more often than not. The Examiner has only provided isolated examples in which mutations can sometimes result in a shift of the biological activity of a naturally occurring polypeptide to a related biological activity found in other members of the polypeptide family. In contrast, the references of Brenner et al. and Bork present findings which are generally applicable to the accuracy and reliability of sequence analysis methods because these references have compiled the results of many such experiments. As such, one of skill in the art would more likely than not believe that GPx6 has the utilities of the family of glutathione peroxidase proteins.

There is, in addition, further evidence that the polypeptide encoded by the claimed polynucleotides has the biological functions of the glutathione peroxidase family. For example, the specification discloses that “PFAM identifies significant sequence identity with glutathione peroxidase” and that “BLOCKS identifies significant sequence identity with glutathione peroxidase over residues 35-60, 63-100, 107-133, and 138-159, which includes the glutathione peroxidase catalytic triad formed by residues Cys57, Gln92, and Trp142” (Specification; page 13, lines 18-21). The Examiner has stated that “despite the chemical and structural similarities shared between GPx6 and phospholipid hydroperoxide glutathione peroxidase, there is still a difference and it cannot be predicted, based on the information in the specification, what affect [sic] this difference has on the function of the protein” (Office Action, November 6, 2002; page 5; emphasis in original). To the contrary. The identification of particular portions of GPx6 which are likely to be important to the functioning of GPx6 as a glutathione peroxidase, such as the catalytic triad residues Cys57, Gln92, and Trp142, provides a reasonable degree of certainty that GPx6 has the biological functions of glutathione peroxidases.

The identification of particular regions and residues of GPx6 as indicators that GPx6 is a glutathione peroxidase provides independent confirmation of the results of the sequence comparison between GPx6 and GPx4. None of these features of GPx6 have been adequately considered by the Examiner. The disclosure of the instant application shows that a relationship between GPx6 and

glutathione peroxidase proteins is justified, and that one of skill in the art would reasonably conclude that GPx6 has the biological functions of glutathione peroxidase proteins based on objective criteria. Therefore, the subject application has adequately disclosed at least one utility of the claimed invention based on the biological function of GPx6 as a glutathione peroxidase. These utilities are in addition to the well established utilities of GPx6 in toxicology testing and drug discovery, which are not dependent on the specific biological function of GPx6.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be reversed for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the polypeptide encoded by the claimed polynucleotides is in fact a member of the family of glutathione peroxidases, which are known to have specific utility.

**IV. By requiring the Appellants to assert a particular or unique utility, the Patent Examination Utility Guidelines and Training Materials applied by the Patent Examiner misstate the law**

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website [www.uspto.gov](http://www.uspto.gov), March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities, which meet the statutory requirements, and “general” utilities, which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” i.e., unique (Training Materials at page 52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”).)

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus incredible “throwaway” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard. Karen Hall, Genomic Warfare, *The American Lawyer* 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was

determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B (*Montedison*, 664 F.2d at 374-375).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

**Issue 2 – Whether claims 3-6, 9-11, 38, 39, 42, and 43 meet the written description requirement of 35 U.S.C. § 112, first paragraph**

Claims 3-6, 9-11, 38, 39, 42, and 43 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that “for the applicant to be entitled to the genus of variants that are 90% identical to SEQ ID No:2, applicant must disclose a representative number of sequences that correspond the genus of variants. The specification has not disclosed any of this information, and therefore, the applicant is only entitled to what was in their possession at the time of filing” (Office Action, May 23, 2003; page 7). This rejection is traversed.

With respect to this rejection, claims 4, 10, 38, and 42 are separately patentable from claims 3, 5, 6, 9, 11, 39, and 43, because claims 4, 10, 38, and 42 are directed to inventions defined by the polynucleotide sequence of SEQ ID NO:2 and/or the amino acid sequence of SEQ ID NO:1. In particular, claims 4, 10, and 42 are drawn to polynucleotides comprising SEQ ID NO:2, and complements and RNA variants thereof. Claim 38 is drawn to polynucleotides encoding a polypeptide



comprising SEQ ID NO:1. The Examiner's rejection is based on the alleged lack of written description of polynucleotide variants and of polynucleotides encoding polypeptide variants, and thus should not apply to claims 4, 10, 38, and 42. For at least this reason, this rejection of claims 4, 10, 38, and 42 should be overturned.

With respect to this rejection, claims 3, 5, 6, 9, 11, 39, and 43 are separately patentable from claims 4, 10, 38, and 42, because claims 3, 5, 6, 9, 11, 39, and 43 are directed to inventions, which include polynucleotide and polypeptide variants, for which the application as filed provides an adequate written description. For at least this reason, this rejection of claims 3, 5, 6, 9, 11, 39, and 43 should be overturned.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

... the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.  
*Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

**A. The specification provides an adequate written description of the claimed “variants” of SEQ ID NO:1 and SEQ ID NO:2.**

The subject matter encompassed by claims 3-6, 9-11, 38, 39, 42, and 43 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the “variant” language of independent claim 3 recites a polynucleotide encoding a polypeptide “comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.” Similarly, the “variant” language of independent claim 9 recites “a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2.” The amino acid sequence of SEQ ID NO:1 and the polynucleotide sequence of SEQ ID NO:2 are explicitly disclosed in the specification. See, for example, the Sequence Listing and Figures 1A, 1B, and 1C. Variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 3, lines 4-10 and 16-20; page 5, line 33 to page 6, line 24; page 12, line 28 to page 13, line 2; page 13, lines 29-32; page 14, lines 2-28; page 17, lines 17-20; and page 34, lines 8-12.

One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 90% identical to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:1. Given any naturally occurring polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:2, and whether it encoded a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:2 and polynucleotides encoding the recited polypeptide variants of SEQ ID NO:1.

**1. The present claims specifically define the claimed genus through the recitation of chemical structure**

Court cases in which “DNA claims” have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

In claims to genetic material, however, a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA,” without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; i.e., “an mRNA of a vertebrate, which mRNA encodes insulin” in *Lilly*, and “DNA which codes for a human fibroblast interferon-beta polypeptide” in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 9 recites chemical structure to define the claimed genus:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
  - a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
  - b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1,
  - c) a polypeptide fragment comprising at least 14 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said polypeptide fragment has glutathione peroxidase activity, and
  - d) an immunogenic fragment comprising at least 14 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:1.
  
9. An isolated polynucleotide selected from the group consisting of:
  - a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
  - b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
  - c) a polynucleotide complementary to the polynucleotide of a),
  - d) a polynucleotide complementary to the polynucleotide of b), and
  - e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present

claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polynucleotides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry “on whatever is now claimed,” the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

The Patent Office Guidelines indicate that evidence that Appellants were in possession of the claimed invention can include “complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics” (P.T.O. Guidelines, *supra*; emphasis added). The claimed polynucleotides have been described by chemical structure (e.g., relation of the recited polynucleotides to SEQ ID NO:2, relation of the recited polypeptides to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited variant sequences), and chemical properties (e.g., glutathione peroxidase activity or immunogenic activity of the recited polypeptide variants and fragments). Therefore, the written description requirement has been met.

## **2. The present claims do not define a genus which is “highly variant”**

Furthermore, the claims at issue do not describe a genus which could be characterized as “highly variant.” Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner’s attention is directed to the enclosed reference by Brenner et al. (“Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships,” Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner

et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that  $\geq 40\%$  identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polynucleotides encoding glutathione peroxidase proteins, including polynucleotides encoding glutathione peroxidase proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as glutathione peroxidase proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The “variant language” of the present claims recites a polynucleotide encoding “a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1” (note that SEQ ID NO:1 has 187 amino acid residues). This variation is far less than that of polynucleotides encoding all potential glutathione peroxidase proteins related to SEQ ID NO:1, i.e., those glutathione peroxidase proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

**3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications**

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The ‘525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the “dark ages” of recombinant DNA technology.

The present application has a priority date of June 1, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these

remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants, and the claimed polynucleotides encoding the recited polypeptide variants, at the time of filing of this application.

#### **4. Summary**

The Examiner failed to base the written description inquiry “on whatever is now claimed.” Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be overturned.

#### **(9) CONCLUSION**

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of “lack of specificity,” as set forth by the Examiner and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the

claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The written description rejections should also be reversed, based on at least the arguments presented above.

Due to the urgency of this matter, and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

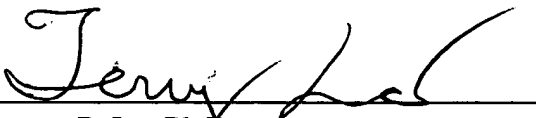
**This brief is enclosed in triplicate.**

Respectfully submitted,

INCYTE CORPORATION

Date:

Oct. 21, 2003.



Terence P. Lo, Ph.D.

Limited Recognition (37 C.F.R. § 10.9(b) ) attached  
Direct Dial Telephone: (650) 621-8581

**Customer No.: 27904**

3160 Porter Drive

Palo Alto, California 94304

Phone: (650) 855-0555

Fax: (650) 849-8886



**APPENDIX**

Claims on appeal:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
  - a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
  - b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1,
  - c) a polypeptide fragment comprising at least 14 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said polypeptide fragment has glutathione peroxidase activity, and
  - d) an immunogenic fragment comprising at least 14 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:1.
4. An isolated polynucleotide of claim 3, comprising the polynucleotide sequence of SEQ ID NO:2.
5. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
6. A cell transformed with a recombinant polynucleotide of claim 5.
9. An isolated polynucleotide selected from the group consisting of:
  - a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
  - b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
  - c) a polynucleotide complementary to the polynucleotide of a),

- d) a polynucleotide complementary to the polynucleotide of b), and
- e) an RNA equivalent of a)-d).

10. An isolated polynucleotide of claim 9 comprising the polynucleotide sequence of SEQ ID NO:2.

11. An isolated polynucleotide comprising at least 30 contiguous nucleotides of a polynucleotide selected from the group consisting of:

- a) a polynucleotide consisting of the polynucleotide sequence of SEQ ID NO:2,
- b) a polynucleotide consisting of a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
- c) a polynucleotide complementary to the polynucleotide of a),
- d) a polynucleotide complementary to the polynucleotide of b), and
- e) an RNA equivalent of a)-d).

38. An isolated polynucleotide of claim 3, encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

39. A polynucleotide of claim 11, comprising at least 60 contiguous nucleotides of a polynucleotide selected from the group consisting of:

- a) a polynucleotide consisting of the polynucleotide sequence of SEQ ID NO:2,
- b) a polynucleotide consisting of a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
- c) a polynucleotide complementary to the polynucleotide of a),
- d) a polynucleotide complementary to the polynucleotide of b), and
- e) an RNA equivalent of a)-d).

42. An isolated polynucleotide of claim 9, selected from the group consisting of:

- a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
- b) a polynucleotide complementary to the polynucleotide of a), and
- c) an RNA equivalent of a)-b).

43. An isolated polynucleotide of claim 3, encoding a polypeptide selected from the group consisting of:

- a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and
- b) a polypeptide comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has glutathione peroxidase activity.